

Pergolide use in Parkinson disease is associated with cardiac valve regurgitation

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Abstract—Objective: To determine if pergolide injures heart valves, by comparing echocardiographic findings in pergolide-treated patients with those of a historical control group. **Methods:** Letters were sent to all patients in the authors' practice believed to be taking pergolide, and those responders who wished to continue it were urged to undergo echocardiography. Echocardiograms were obtained on 46 patients, and scores for valvular regurgitation were compared with those from an age-matched control group derived from the Framingham Study. The composite valve regurgitation score was modeled as a linear function of total milligrams lifetime use of pergolide, controlling for age. **Results:** Eighty-nine percent of pergolide-treated patients had some degree of valvular insufficiency. For each of the three valves for which there are control data, we found an approximately 2- to 3-fold increased risk of abnormal valves in the pergolide patients (odds ratio [OR] \approx 3) and an estimated 14-fold increased risk of concerning tricuspid regurgitation (OR = 18.4). The composite valve score (the sum of valve scores for each of the four valves) was a function of lifetime pergolide use. **Conclusion:** Pergolide may injure cardiac valves, resulting most commonly in tricuspid regurgitation.

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In December 2002, three pergolide-treated patients with serious and unusual heart valve disease were reported.¹ Severe tricuspid insufficiency was the major echocardiographic abnormality, and on pathologic examination, valve thickening was seen, resembling that associated with carcinoid syndrome and fenfluramine. The authors suggested that pergolide might cause heart valve disease in addition to the previously recognized but uncommon complications of retroperitoneal, pericardial, or pleural fibrosis.^{2–4} Subsequently, it was reported that 12 patients with pergolide-associated valvular heart disease (PAVHD) had been registered by the Food and Drug Administration (FDA).⁵ In 10 of these cases, valvular insufficiency was noted. More recently, 10 patients were reported with echocardiographic evidence of valvular insufficiency on high-dose therapy with pergolide, 2 of whom had severe cardiac symptoms.⁶ None of these reports compared pergolide-treated patients with a control group, and thus none could address whether PAVHD is a very low probability outcome outweighed by the expected benefits from treatment or a considerably higher likelihood event in which case risks might exceed benefits. We studied the prevalence of heart valve disease in our patients using pergolide vs historical controls.

Methods. Subjects. The clinical database of the Clinical Center for Movement Disorders at the University of Texas Southwest-

ern Medical School, which lists medications continued or initiated at the most recent visit, was queried in January 2003 for all patients listed as taking pergolide who were seen since 1994. A letter outlining the newly raised concern about PAVHD was mailed to the 257 patients so identified, along with a response sheet and self-addressed stamped envelope. The options described by the letter were to continue taking pergolide despite the concern, in which case they should discuss with their physicians the advisability of a screening echocardiogram, or to cease the pergolide with the option of replacement using a non-ergot-derived dopamine agonist (ropinirole or pramipexole). When no response was received, phone calls were made to available telephone numbers, and new contact information was sought from the university's records system. The institutional review board approved the study.

Echocardiography interpretation. Echocardiographic reports were reviewed for valvular regurgitation. Descriptive terms for the degree of regurgitation were converted to numerical values for analysis as follows: trace = 1, mild = 2, moderate = 3, and severe = 4. If regurgitation was said to be absent or no comment was made about a particular valve, the regurgitation score was set to 0. Three reports indicated intermediate degrees of regurgitation (e.g., mild to moderate), in which case a score of 2.5 was assigned. Thickening was recorded present if reported and absent if not. To determine the appropriateness of comparing these clinical valve regurgitation scores with those reported in the Framingham Heart Study⁷ (our historical control group), one of us reviewed the tapes of all 23 echocardiograms performed at University of Texas Southwestern (while blinded to valve scores on the official reports), rating regurgitation according to the method described in this article.⁷ These scores were found to have very good concordance with those derived from the official reports (weighted κ = 0.65).

Control data. The Framingham Heart Study provided prevalence data for trace, mild, and moderate or worse regurgitation of

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Table 1 Percentage of patients (controls)* with certain valve regurgitation grades

Valve regurgitation grade	Mitral	Aortic	Tricuspid	Pulmonary
0	30.4 (10.2)	56.5 (79.8)	28.3 (16.8)	84.8
1	20.3 (62.8)	10.9 (9.3)	23.9 (59)	6.5
2	34.8 (22.7)	23.9 (9.6)	29.3 (20.5)	8.7
3 or 4	14.1 (4.3)	8.7 (1.2)	18.5 (1.2)	0

* Control data not available for pulmonic valve regurgitation.

tricuspid, mitral, and aortic valves using data from over 3,000 subjects.⁷ The prevalence of each category of regurgitation was reported per valve, per sex, and per decade of life. These prevalence tables were used to calculate control probabilities of trace, mild, or moderate or worse regurgitation for each valve for each individual in our cohort. These probabilities were summed to calculate the expected number of regurgitation cases in a control cohort with the age, sex structure, and size of our study group.

Statistics. Odds ratios (ORs) for mitral (MR), tricuspid (TR), and aortic (AR) valve regurgitation were calculated for the pergolide cohort as compared with the control group. Two outcomes were compared: 1) the presence of nonphysiologic valvular regurgitation as defined by the Framingham Study,⁷ herein referred to as abnormal regurgitation (AR \geq trace severity, MR \geq mild severity, and TR \geq mild severity); and 2) the presence of clinically significant regurgitation using criteria similar to those employed by the FDA in the fenfluramine/phentermine studies,⁸ herein referred to as concerning regurgitation (AR \geq mild severity, MR \geq moderate severity, and TR \geq moderate severity). The composite valve regurgitation score (the sum of individual valve scores for the four valves of each patient) was modeled as a linear function of total milligrams lifetime use of pergolide (transformed to square root to normalize the distribution), controlling for age. The presence of thickening of any valve was modeled as a function of lifetime pergolide use and age using logistic regression.

Results. No patients who were last seen before June 15, 2001, could be confirmed to be still taking pergolide: Ten had died, 8 were contacted and reported that they were no longer taking this drug, and no contact could be made with the remaining 124 past (and possibly continuing) pergolide users who had not been seen in nearly 2.5 years at the time we completed our data analysis. More meaningful follow-up data are available for patients seen since June 2001 who were listed in the database as taking pergolide (n = 115): Two had died, 11 had stopped taking pergolide prior to publicity surrounding PAVHD, and 20 were not

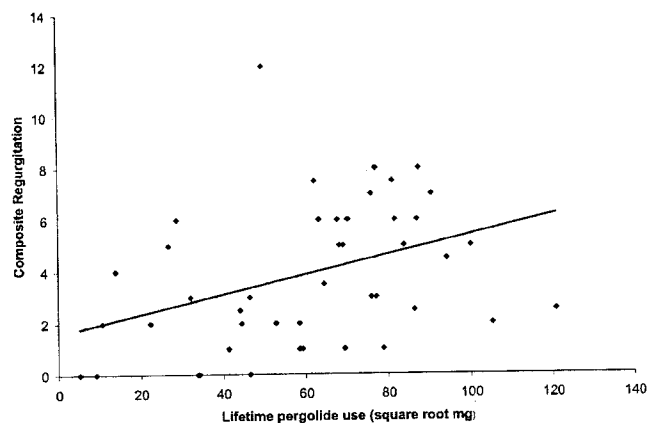


Figure. Composite valve score as a function of lifetime pergolide use.

reached, leaving 82 patients that we could confirm were taking pergolide at the time of our letter. Further analysis is limited to these and the three patients who subsequently entered the practice taking pergolide prescribed by another physician. Of these 85, echocardiographic data were available for 46 patients. These had a mean age of 67 (range 40 to 89), and 34 were men. All but three patients with restless legs syndrome were using pergolide to treat Parkinson disease (PD).

Some degree of valve regurgitation was present in one or more valves of 41 patients (89%). The percentage of patients with each grade of regurgitation per valve is shown in table 1, along with the prevalence in an age-matched, sex-matched cohort based on the control data. Table 2 shows the ORs for abnormal regurgitation and for concerning regurgitation. For each of the three valves for which there are control data, we found an approximately 2- to 3-fold increased risk of abnormal valves in the pergolide patients (OR = 2.6 to 4.0) and an estimated 14-fold increased risk of concerning tricuspid regurgitation (OR = 18.4).

The composite valve score ranged from 0 through 8 with an outlier at 12. The composite was a function of lifetime pergolide use ($r^2 = 0.1374$). The relationship is shown in the figure.

Valve thickening was documented in 15 patients, among whom 1 tricuspid valve, 12 aortic valves, and 9 mitral valves were thickened. Presence of one or more

Table 2 Number of patients* and controls with abnormal and concerning regurgitation with calculated odds ratios and p values

	Pergolide, n = 46	Controls, n = 46	Odds ratio (95% CI)	p Value
Abnormal† mitral regurgitation	22.5	12.4	2.6 (1.1–6.2)	0.03
Abnormal aortic regurgitation	20	9.7	3.0 (1.3–7.7)	0.01
Abnormal tricuspid regurgitation	22	10	3.3 (1.3–8.2)	0.02
Concerning‡ mitral regurgitation	6.5	2	3.7 (0.7–19.2)	0.12
Concerning aortic regurgitation	15	5	4.0 (1.3–12.2)	0.04
Concerning tricuspid regurgitation	8.5	0.6	18.4 (1.2–283)	0.02

* Fractional number of patients resulted from adding fractional valve scores.

† Abnormal regurgitation = AR \geq trace severity, MR \geq mild severity, and TR \geq mild severity.

‡ Concerning regurgitation = AR \geq mild severity, MR \geq moderate severity, and TR \geq moderate severity.

AR = aortic regurgitation; MR = mitral regurgitation; TR = tricuspid regurgitation.

thickened valves was not associated with lifetime pergolide ingestion on logistic regression ($p = 0.6$).

Case reports. The following case reports were not typical of our study cohort but are presented to demonstrate the potential for a clinically serious cardiac outcome from chronic pergolide treatment.

Patient 1. This 61-year-old man was diagnosed with PD in 1993 and began pergolide in 1997. In 1999, he developed a heart murmur, and echocardiography showed mild to moderate aortic insufficiency and mild mitral and tricuspid regurgitation. Two years later, repeat echocardiography showed the aortic and mitral regurgitation had reached moderate severity. Six years after beginning pergolide, an echocardiogram revealed that his aortic insufficiency had progressed to the moderate to severe range, with no change in the mitral and tricuspid regurgitation. At this time, pergolide was stopped. A follow-up echocardiogram 7 months later showed improvement in both aortic and mitral valves (composite valve score on pergolide = 7.5, composite valve score 7 months after cessation of treatment = 5).

Patient 2. This 78-year-old man developed PD in 1997 and began pergolide 2 years later. After 3 years on this agent, an echocardiogram performed to evaluate hypertension revealed thickening of the aortic, mitral, and tricuspid valves along with mild to moderate mitral valve regurgitation and severe tricuspid regurgitation. Six months later, he developed abdominal and lower extremity edema. He underwent a right heart catheterization, which showed restrictive–constrictive physiology. Endomyocardial biopsy was nondiagnostic. Cardiac MRI showed a thickened pericardium suggestive of constrictive pericarditis, and he underwent pericardectomy and stopped pergolide. Postoperatively, the patient’s cardiac symptoms resolved.

Patient 3. This 69-year-old man with PD began therapy with ropinirole and levodopa in 1997. Two years later, he was switched from ropinirole to pergolide owing to hallucinations, which resolved following the switch. Four years later, an echocardiogram was performed that showed mild mitral and pulmonic regurgitation and severe tricuspid regurgitation, prompting a switch from pergolide to pramipexole. Several months later, he presented with abdominal bloating, increased shortness of breath, confusion, restlessness, and pedal edema. Repeat cardiac echo showed improvement in his tricuspid regurgitation from severe to mild. Right heart catheterization demonstrated restrictive physiology. He subsequently underwent a CT scan of the chest, myocardial biopsy, and fat-pad biopsy, which were negative for amyloidosis, sarcoidosis, hemachromatosis, and hemosiderosis. His final diagnosis was idiopathic restrictive cardiomyopathy.

Patient 4. This 75-year-old man was diagnosed with PD in 1999. At that time, he began therapy with ropinirole but was switched to pergolide the following year because of nausea and diminished efficacy. An echocardiogram done in 2000 was notable only for mild aortic regurgitation. In April 2001, he became dyspneic and was found to have syncope in the setting of a normal ejection fraction. He had a pacemaker placed in January 2002 to manage arrhythmia.

In April of that year, he was admitted to the hospital with severe decompensated heart failure and severe mitral regurgitation. Pergolide treatment was discontinued, and amiodarone was begun. His rhythm was normalized with resolution of dyspnea. On a follow-up echocardiogram, his mitral regurgitation had improved considerably.

Discussion. Pergolide is a widely used drug; since 1989, an estimated 500,000 people have been treated with this agent, mostly for PD.⁹ Rare cases of retroperitoneal, pericardial, or pleural fibrosis have long been considered the most serious potential complications of pergolide use.²⁻⁴ In the last year, cases of PAVHD have been reported, but without any estimate of the prevalence of the association.^{1,5,6} Here, we report a high prevalence of PAVHD; potentially serious valve disease was present in >44% of our patients taking pergolide who had echocardiograms. However, as the most common concerning valvular abnormality in our series was mild to moderate aortic insufficiency, which often carries a benign prognosis, it is unclear what percentage of these patients would progress to develop disabling heart disease. The ORs demonstrate that pergolide may damage heart valves, and the high prevalence of valvular disease in our pergolide-treated patients suggests that this may be a common problem. Based on this finding, we have recommended that all remaining patients come off pergolide, and we do not plan to initiate therapy with this drug in new patients unless its safety with respect to valvular heart disease can be demonstrated. Several patients chose to remain on pergolide in spite of our findings, in most cases because the drug had been effective for their symptoms of PD and they had not done as well on alternate dopamine agonists. We asked all patients who chose to remain on pergolide to sign a consent document outlining our concerns, and we plan to follow this small group with echocardiograms to be done at least annually.

Because of methodologic limitations inherent in our study design, the implications of our findings are not conclusive. For instance, 23 of 46 echocardiograms were performed at other centers by a variety of cardiologists, and the interobserver concordance was not determined. Echocardiographers may have been more inclined in our cohort as compared with the control group to overread regurgitation, because the test requisition was for a drug-related complication with unspoken but unavoidable medicolegal implications. We have no echocardiographic data on the 46% of our patients who qualified for the study based on pergolide use at the index time but who declined to undergo examination or for whom no examination was ordered because they simply terminated pergolide use when the concern was raised. Similarly, we have no data on the large number of patients registered in our database as users of pergolide who were lost to follow-up. However, there is no basis for believing that the prevalence of valve disease was higher or lower in these unevaluated populations.

Finally, a conceptually ideal control group (PD patients treated with dopaminergic drugs but not on pergolide) with echocardiographic data was not available.

The biologic mechanism by which pergolide might cause valve disease is unknown, but it is noteworthy that similar valvular lesions have been reported in patients with migraine headache taking ergot alkaloids such as ergotamine and methysergide.¹⁰ It has been suggested that a state of serotonin excess induced by agonist interactions with serotonin receptors, especially the 5-HT_{2B} receptor, may be responsible for the cardiotoxic effects of some anorectic agents.^{11,12} High serotonin levels have been shown to correlate with valve lesions in carcinoid heart disease.¹³ Pergolide, in addition to its known dopaminergic properties, has been reported to have agonist properties at some serotonergic 5-HT receptors¹⁴ and thus might cause valvular heart disease through a similar serotonergic mechanism.

In addition to valvular regurgitation noted in our patients, two patients developed restrictive–constrictive cardiac pathologies while on treatment with pergolide. Patient 2 had fibrosis of the pericardium after having taken pergolide for 50 months, and Patient 3 had fibrosis of the myocardium after having taken pergolide for 44 months. The precise etiology of the condition in these cases is unknown, but as pergolide has been reported in association with other fibrotic complications, it is possible that the drug and the observed cardiac disease were related in these cases. It is unknown whether the valvular disease seen in these two patients was secondary to pergolide use or to the restrictive cardiac disease itself.

The natural history of PAVHD remains to be clarified. Three of our patients developing clinically disabling heart disease have improved echocardiographically with cessation of pergolide, but long-term outcome data from those stopping this drug are not currently available. We plan to obtain repeat echocardiography in those patients with abnormal valves 6 to 12 months after stopping pergolide to address this important clinical question. If the natu-

ral history of fenfluramine/phentermine-associated heart valve disease is any guide, then perhaps the echocardiographic improvement seen in three of our patients will be observed routinely.¹⁵ In light of our findings, we believe that dopamine agonist therapy should be initiated with a nonergot drug and that in those currently taking pergolide, consideration should be given to switching to a nonergot agonist until the safety of pergolide can be firmly established.

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